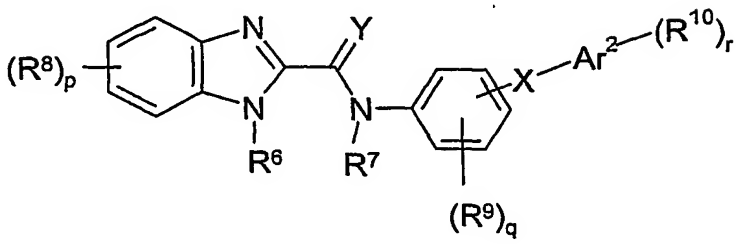
Claims

1. Benzimidazole carboxamides of formula I



I

wherein

R^6, R^7 are independently from one another H, A or SO_2A,

A is independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, alkoxy and alkoxyalkyl,

Ar^2 is selected independently from one another from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or two heteroatoms, independently selected from N, O and S,

R^8, R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, $C(Hal)_3$, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nOR^{11}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOOR^{12}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$,

$(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, CH=N-OA, CH_2CH=N-OA, $(CH_2)_nNHOA$, $(CH_2)_nCH$=N-R^{11}, $(CH_2)_nOC(O)NR^{11}R^{12}$, $(CH_2)_nNR^{11}COOR^{12}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$, $C(R^{13})HCOR^{12}$, $(CH_2)_nN(R^{11})CH_2CH_2N(R^{12})CH_2COOR^{12}$, $(CH_2)_nN(R^{11})CH_2CH_2NR^{11}R^{12}$, CH=$CHCOOR^{11}$, CH=$CHCH_2NR^{11}R^{12}$, CH=$CHCH_2NR^{11}R^{12}$, CH=$CHCH_2OR^{13}$, $(CH_2)_nN(COOR^{11})COOR^{12}$, $(CH_2)_nN(CONH_2)COOR^{11}$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^{11})COOR^{12}$, $(CH_2)_nN(CH_2CONH_2)COOR^{11}$, $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{11}$, $(CH_2)_nCHR^{13}COOR^{11}$, $(CH_2)_nCHR^{13}CH_2OR^{14}$, $(CH_2)_nOCN$ and $(CH_2)_nNCO$, wherein

R^{11}, R^{12} are independently selected from a group consisting of H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$, or in $NR^{11}R^{12}$,

R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7-membered heterocyclus which optionally contains 1 or 2 additional hetero atoms, selected from N, O an S,

R^{13}, R^{14} are independently selected from a group consisting of H, Hal, A, $(CH_2)_mAr^4$ and $(CH_2)_mHet$,

Ar^3, Ar^4 are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group

consisting of A, Hal, NO_2, CN, OR^{15}, $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15}, $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,

Het is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one ore more substituents, selected from a group consisting of A, Hal, NO_2, CN, OR^{15}, $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15}, $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,

R^{15}, R^{16} are independently selected from a group consisting of H, A, and $(CH_2)_mAr^6$, wherein

Ar^6 is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH_2 and CF_3,

k, m and n are independently of one another 0, 1, 2, 3, 4, or 5,

X represents a bond or is $(CR^{11}R^{12})_h$, or $(CHR^{11})_h$-Q-$(CHR^{12})_i$, wherein

Q is selected from a group consisting of O, S, N-R^{15}, $(CHal_2)_j$, $(O\text{-}CHR^{18})_j$, $(CHR^{18}\text{-}O)_j$, $CR^{18}=CR^{19}$, $(O\text{-}CHR^{18}CHR^{19})_j$, $(CHR^{18}CHR^{19}\text{-}O)_j$, C=O, C=S, $C=NR^{15}$, $CH(OR^{15})$, $C(OR^{15})(OR^{20})$, C(=O)O, OC(=O), OC(=O)O, $C(=O)N(R^{15})$, $N(R^{15})C(=O)$, OC(=O)$N(R^{15})$, $N(R^{15})C(=O)O$, CH=N-O, $CH=N\text{-}NR^{15}$, S=O, SO_2, SO_2NR^{15} and $NR^{15}SO_2$, wherein

R^{18}, R^{19}, R^{20} are independently selected from the meanings given for R^8, R^9 and R^{10}, preferably independently selected from the group consiting of H, A, Hal, CH_2Hal, $CH(Hal)_2$, $C(Hal)_3$, NO_2, $(CH_2)_nCN$, $(CH_2)_nOR^{11}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, $(CH_2)_nNHOA$ and $(CH_2)_nNR^{11}COOR^{13}$,

h, i are independently from each other 0, 1, 2, 3, 4, 5, or 6, and

j is 1, 2, 3, 4, 5, or 6,

Y is selected from O, S, NR^{21}, $C(R^{22})$-NO_2, $C(R^{22})$-CN and $C(CN)_2$, wherein

R^{21} is independently selected from the meanings given for R^{13}, R^{14} and

R^{22} is independently selected from the meanings given for R^{11}, R^{12},

p, r are independently from one another 0, 1, 2, 3, 4 or 5,

q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,

u is 0, 1, 2 or 3, preferably 0, 1 or 2,

and

Hal is independently selected from a group consisting of F, Cl, Br and I;

the tautomeric forms therof; and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof.

2. Benzimidazole carboxamide according to claim 1, wherein

Ar^2 is selected from aromatic hydrocarbons containing 6 to 10 and especially 6 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 8 and especially 4 to 6 carbon atoms and one or two heteroatoms, independently selected from N, O and S and especially selected from N and O,

R^8, R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, $C(Hal)_3$, NO_2, $(CH_2)_nCN$, $(CH_2)_nOR^{11}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, $(CH_2)_nNHOA$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^8$, $(CH_2)_nN(R^{11})$, $C(R^{13})HCOR^8$, $(CH_2)_nN(COOR^{13})COOR^{14}$, $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$, $(CH_2)_nN(CH_2CONH_2)COOR^{13}$, $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$, $(CH_2)_nCHR^{13}COOR^{14}$ and $(CH_2)_nCHR^{13}CH_2OR^{14}$,

X represents a bond or is $(CR^{11}R^{12})_h$, or $(CHR^{11})_h$-Q-$(CHR^{12})_i$, wherein

Q is selected from a group consisting of O, S, N-R^{15}, $(CHal_2)_j$, (O-$CHR^{18})_j$, $(CHR^{18}$-O$)_j$, CR^{18}=CR^{19}, (O-$CHR^{18}CHR^{19})_j$, $(CHR^{18}CHR^{19}$-O$)_j$, C=O, C=NR^{15}, $CH(OR^{15})$, $C(OR^{15})(OR^{20})$, $C(=O)N(R^{15})$, $N(R^{15})C(=O)$, CH=N-NR^{15}, S=O, SO_2, SO_2NR^{15} and $NR^{15}SO_2$, wherein

h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6, preferably 0, 1, 2 or 3 and

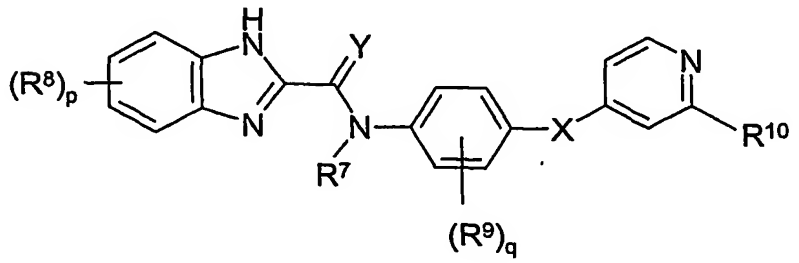
j is 1, 2, 3, 4, 5 or 6, preferably 1, 2, 3 or 4,

p is 1, 2, 3 or 4, preferably 1, 2 or 3, and

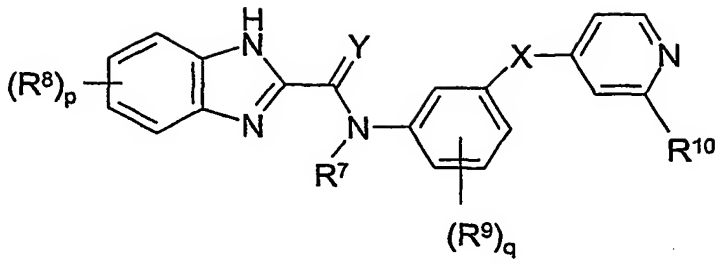
r is 0, 1, 2, or 3, preferably 0, 1 or 2;

the tautomeric forms therof; and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof.

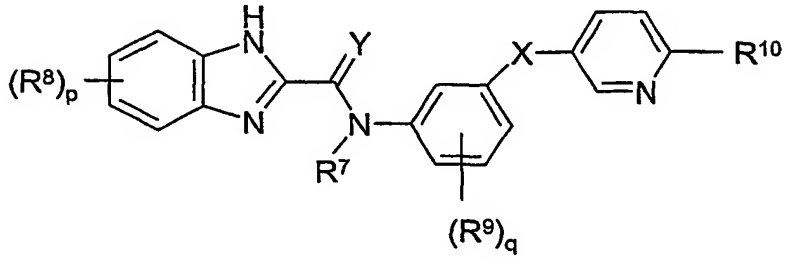
3. Benzimidazole carboxamide according to claim 1 or 2, selected from the compounds of the formulae Ia, Ib, Ic and Id,



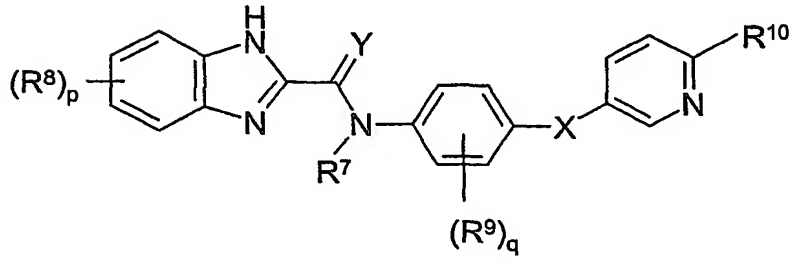
Ia



Ib



Ic



Id

wherein

R^8, p, X, Y, R^9 and q are as defined in claims 1 or 2, and R^{10} is H or as defined in claims 1 or 2;

the tautomeric forms therof; and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof.

4. Benzimidazole carboxamide according to claim 3, additionally comprising one or two substituents selected from the group consisting of $O(CH_2)_nNR^{11}R^{12}$, $NR^{11}(CH_2)_nNR^{11}R^{12}$, $O(CH_2)_nOR^{12}$ and $NR^{11}(CH_2)_nOR^{12}$,

wherein

R^{11}, R^{12} are independently selected from a group consisting of H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$, or in $NR^{11}R^{12}$,

R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7-membered heterocyclus which optionally contains 1 or 2 additional hetero atoms, selected from N, O an S, and

n is 1, 2, 3, 4, 5 or 6.

5. Benzimidazole carboxamide according to one of the claims 1 to 4, selected from the compounds (1) to (128) of table 1; the tautomeric forms therof; and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof.

6. Benzimidazole carboxamide according to one of the claims 1 to 5 as a medicament.

7. Benzimidazole carboxamide according to one of the claims 1 to 5 as a kinase inhibitor.

8. Benzimidazole carboxamide according to claim 7, characterized in that the kinases are selected from raf-kinases and VEGFR kinases.

9. Pharmaceutical composition, characterized in that it contains one or more compounds according to one of the claims 1 to 5.

10. Pharmaceutical composition according to claim 9, characterised in that it contains one or more additional compounds, selected from the group consisting of physiologically acceptable excipients, auxiliaries,

adjuvants, carriers and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 5.

11. Process for the manufacture of a pharmaceutical composition, characterised in that one or more compounds according to one of the claims 1 to 5 and one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 5, is processed by mechanical means into a pharmaceutical composition that is suitable as dosageform for application and/or administration to a patient.

12. Use of a compound according to one of the claims 1 to 5 as a pharmaceutical.

13. Use of a compound according to one of the claims 1 to 5 in the treatment and/or prophylaxis of disorders.

14. Use of a compound according to one of the claims 1 to 5 for producing a pharmaceutical composition for the treatment and/or prophylaxis of disorders.

15. Use according to claim 13 or 14, characterised in that the disorders are caused, mediated and/or propagated by kinases selected from raf-kinases and VEGFR kinases.

16. Use according to claim 13, 14 or 15, characterised in that the disorders are selected from the group consisting of hyperproliferative and nonhyperproliferative disorders.

17. Use according to claim 13, 14, 15 or 16, characterised in that the disorder is cancer.

18. Use according to claim 13, 14, 15 or 16, characterised in that the disorder is noncancerous.

19. Use according to claim 13, 14, 15, 16 or 18, characterised in that the noncancerous disorders are selected from the group consisting of infections, psoriasis, arthritis, inflammation, endometriosis, scarring, begnin prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.

20. Use according to one of the claims 13 to 17, characterised in that the disorders are selected from the group consisting of brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia.

21. Use according to one of the claims 13 to 16 and 18, characterised in that the disorders are selected from the group consisting of arthritis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation and neurodegenerative diseases.

22. Use according to one of the claims 13 to 18, characterised in that the disorders are selected from the group consisting of rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease,

inflammation, renal disease and angiogenesis disorders.

23. Use of a compound according to one of the claims 1 to 5 as a kinase inhibitor.

24. Use according to claim 23, characterised in that the kinase is one or more raf-kinases, selected from the group consisting of A-Raf, B-Raf and Raf-1.

25. Method for the treatment and/or prophylaxis of disorders, characterised in that one or more compounds according to one of the claims 1 to 5 is administered to a patient in need of such a treatment.

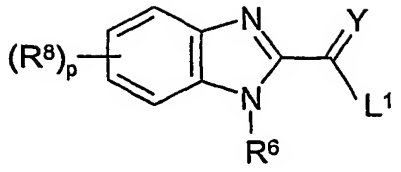
26. Method according to claim 25, characterised in that the one or more compounds according to one of the claims claim 1 to 5 are administered as a pharmaceutical composition according to claim 9 or 10.

27. Method for the treatment and/or prophylaxis of disorders according to claim 26, characterised in that the disorders are as defined in one of the claims 15 to 22.

28. Method for the treatment according to claim 27, characterised in that the disorders is cancerous cell growth mediated by by one or more kinases.

29. Method for producing compounds of formula I, characterised in that

a) a compound of formula II



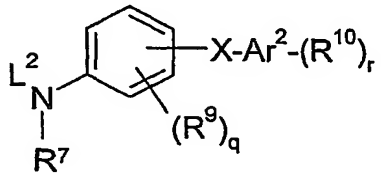
II

wherein

L^1 is Cl, Br, I, OH, an esterified OH-group or a diazonium moiety, and R^6, R^8, p and Y are as defined in claim 1,

is reacted

b) with a compound of formula III,



III

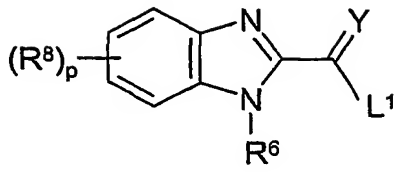
wherein

L^2 is H or a metal ion, and R^7, R^9, q, X, Ar^2, R^{10} and r are as defined in claim 1,

and optionally

c) isolating and/or treating the compound of formula I obtained by said reaction withan acid, to obtain the salt thereof.

30. Compound of formula II,

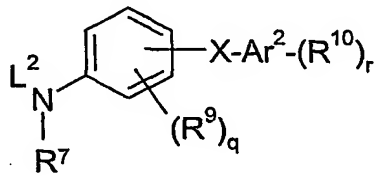


II

wherein

L^1 is Cl, Br, I, OH, an esterified OH-group or a diazonium moiety, and R^6, R^8, p and Y are as defined in claim 1.

31. Compound of formula III,



III

wherein

L^2 is H or a metal ion, and R^7, R^9, q, X, Ar^2, R^{10} and r are as defined in claim 1.